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EDITORIAL

When should I start broad-spectrum antibiotics?

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Broad-spectrum antibiotics are often considered "magic bullets" for treating severe or life-threatening infections when the causative pathogen is unknown. The aim is to provide coverage against a wide range of infections caused by Gram-positive and Gram-negative including resistant pathogens while waiting for culture results. They are considered life-saving drugs especially in clinical settings lacking rapid diagnostic tests. In the intensive care unit (ICU), the urgent need to treat critically ill patients often leads to their overuse. In fact, numerous studies have shown that delays in initiating adequate therapy (defined as using an antibiotic to which the pathogen is susceptible), increased in antimicrobial resistant sepsis [1], and correlate with increased morbidity and mortality [2]. Clinicians therefore often use such agents empirically to ensure that the antibiotic choice covers the causative pathogen(s). However, the indiscriminate use of both old and novel broad-spectrum antibiotics has significantly contributed to the development of antimicrobial resistance (AMR), a critical global health issue [3].

Bacteria develop antibiotic resistance through intrinsic, acquired or adaptive genetic mechanisms [4]. Key contributors to AMR include environmental factors, drug-, and patient-related factors. However, physicians' practice is one of the major reasons in further driving AMR. This selection process is exacerbated by the frequent use of invasive devices, such as ventilators and catheters. Moreover, the ICU environment facilitates the horizontal transfer of resistance genes, further exacerbating the problem. In addition to selecting for AMR, overuse and prolonged use of broad-spectrum antibiotics contributes to increased cost of care, toxicity, and development of *Clostridioides difficile* colitis [5]. Diagnostic stewardship, including the use of new molecular tools, when applied properly and promptly can guide clinicians in the prescription of the broad-spectrum antibiotics only when needed [6].

Potential benefits of broad-spectrum antibiotics

A major modifiable risk factor for adverse outcomes in sepsis is the inappropriateness of initial antibiotic treatment, which often arises from empirical choices failing to cover multidrug-resistant organisms (MDROs) [7]. This observation justifies the recommendation to empirically use broad-spectrum antibiotics targeting all potential causative pathogens, including MDRO, in cases of sepsis, and severe infections such as ventilated hospital-acquired pneumonia (vHAP): the choice of coverage should be guided by the likelihood of MDROs being the causative pathogens and the presence of shock which leaves less room for error. Predicting clinical risk factors for acquiring MDROs in the host and understanding local epidemiologic data in the ICU, including resistance patterns, should guide the empiric antibiotic choice. In some instances, broad-spectrum antibiotic and combination empirical therapy is necessary as a single drug might not be sufficient to address all the risks especially in the most severe patients [8]. Rapid de-escalation with the results of bacteriological exams will reduce antibiotic selection pressure.

Specific circumstances necessitate the use of broad-spectrum antibiotics for targeted therapy against MDROs, including newer ones. Examples include meropenem for bacteremia caused by third-generation cephalosporin-resistant Enterobacterales [9, 10], ceftazidime-avibactam or meropenem–vaborbactam for severe infections caused by carbapenem-resistant Enterobacterales, and ceftolozane-tazobactam for vHAP or infections

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caused by carbapenem-resistant *Pseudomonas aeruginosa* [11]. Additional considerations that may require the use of certain broad-spectrum antibiotics include adequate tissue penetration and pharmacokinetics/pharmacodynamics optimization [12]. For instance, ceftriaxone should be preferred over amoxicillin for community-acquired central nervous system infections, and meropenem over piperacillin–tazobactam for nosocomial central nervous system infections.

Negative impact of broad-spectrum antibiotics

Recent literature suggests that broad initial antimicrobial therapy is associated with poor outcomes. Webb et al. studied 1995 patients with community acquired pneumonia of whom 39.7% received broad-spectrum antibiotics, but only 3% had infections caused by MDRO [13]. After adjusting for confounders, broad-spectrum-antibiotic treatment was associated with increased mortality, linked to a 17.5% rate of antibiotic-associated adverse events among decedents on broad-spectrum antibiotics. In this study where bacteriological samples were often negative, other diseases requiring different treatments may have been missed. In another cohort of 15,183 adults with bacteriologically documented community acquired sepsis, 12,398 (81.6%) received appropriate antibiotics [1]. Less than 30% of cases were due to MDROs. Unnecessary broad-spectrum antibiotics (defined as coverage of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci (VRE) and ceftriaxone-resistant Gram-negative bacteria (GNB) when none of these were isolated) occurred in 8,405 (67.8%) cases. They were also associated with an adjusted odds ratio (OR) of 1.27 (1.06–1.4) for hospital death compared to appropriate broad-spectrum initial antibiotic therapy. An increase in acute kidney injury and *C. difficile* infections were also observed. Data for nosocomial infections also suggest that a single agent is not superior to dual therapy, but does increase antibiotic exposure [14].

Role of rapid diagnostic tests

Although risk factors for MDROS have been extensively reported, none of the available scores can individually predict MDRO infections [15]. However, an early assessment of the risk factors (Fig. 1) allows for the categorization of patients into low, intermediate and high pretest probability groups for MDRO infections. Following this

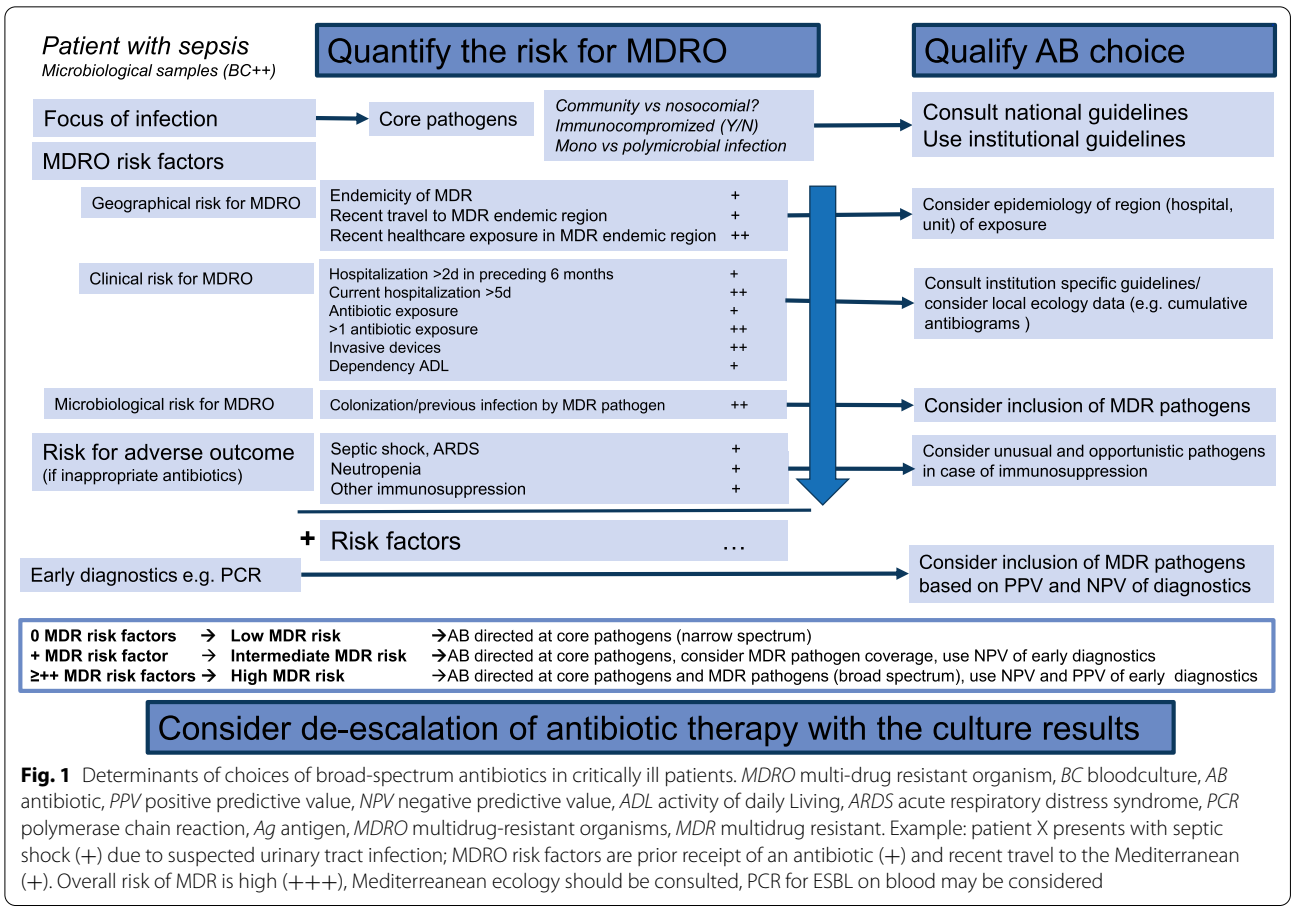
Patient with sepsis
Microbiological samples (BC++)
Quantify the risk for MDRO
Qualify AB choice
Focus of infection
Core pathogens
Community vs nosocomial?
Immunocompromized (Y/N)
Mono vs polymicrobial infection
Consult national guidelines
Use institutional guidelines
MDRO risk factors
Geographical risk for MDRO
Endemicity of MDR +
Recent travel to MDR endemic region +
Recent healthcare exposure in MDR endemic region ++
Consider epidemiology of region (hospital, unit) of exposure
Clinical risk for MDRO
Hospitalization >2d in preceding 6 months +
Current hospitalization >5d ++
Antibiotic exposure +
>1 antibiotic exposure ++
Invasive devices ++
Dependency ADL +
Consult institution specific guidelines/ consider local ecology data (e.g. cumulative antibiograms)
Microbiological risk for MDRO
Colonization/previous infection by MDR pathogen ++
Consider inclusion of MDR pathogens
Risk for adverse outcome
(if inappropriate antibiotics)
Septic shock, ARDS +
Neutropenia +
Other immunosuppression +
Consider unusual and opportunistic pathogens in case of immunosuppression
+ Risk factors …
Early diagnostics e.g. PCR
Consider inclusion of MDR pathogens based on PPV and NPV of diagnostics
0 MDR risk factors → Low MDR risk →AB directed at core pathogens (narrow spectrum)
+ MDR risk factor → Intermediate MDR risk →AB directed at core pathogens, consider MDR pathogen coverage, use NPV of early diagnostics
≥++ MDR risk factors → High MDR risk →AB directed at core pathogens and MDR pathogens (broad spectrum), use NPV and PPV of early diagnostics
Consider de-escalation of antibiotic therapy with the culture results

Fig. 1 Determinants of choices of broad-spectrum antibiotics in critically ill patients. *MDRO* multi-drug resistant organism, *BC* bloodculture, *AB* antibiotic, *PPV* positive predictive value, *NPV* negative predictive value, *ADL* activity of daily Living, *ARDS* acute respiratory distress syndrome, *PCR* polymerase chain reaction, *Ag* antigen, *MDRO* multidrug-resistant organisms, *MDR* multidrug resistant. Example: patient X presents with septic shock (+) due to suspected urinary tract infection; MDRO risk factors are prior receipt of an antibiotic (+) and recent travel to the Mediterranean (+). Overall risk of MDR is high (+++), Mediterreanean ecology should be consulted, PCR for ESBL on blood may be considered

preanalytical phase, rapid diagnostic tests performed on appropriate specimens, should therefore refine targeted therapy and avoid unnecessary broad-spectrum antibiotics [6]. Accurate molecular and non-molecular tests can be made available within a few hours for urinary, respiratory, digestive and neurologic infections. If the pretest probability is low, a negative test will have a very high negative predictive value (NPV). Conversely, if the risk is high, the NPV may not be sufficient to eliminate the risk of MDRO infections. Similarly, in a patient with shock or with rapid clinical deterioration, the NPV might be considered insufficiently high to use narrow spectrum antimicrobials. Subsequently, results of obtained cultures will then be used to streamline or deescalate the initial regimen. On the opposite, If the pretest probability is very low, (or if the clinical status is stabilized), the positive predictive value of a test might be insufficient to accept a positive test as true. For example, in severe pneumonia cases in the ICU, if the risk of OXA-48 Enterobacterales is 0.2%, multiplex polymerase chain reaction (mPCR) will never miss the diagnosis but will overdiagnose it in 37.5% of the cases [16]. The numerous, sometimes undesirable, targets of multiplexed syndromic mPCR panels should be interpreted carefully given the pretest probabilities.

Although many rapid diagnostic tools have been developed with a high diagnostic yield, they are often limited by accessibility, cost, and lack of knowledge regarding their use. Therefore, their implementation should be combined with efforts to improve educational skills and behavior of health-care providers. The role of infectious diseases specialists and microbiologists is crucial in deciding the appropriate empirical therapy.

Take-home message

In the authors' opinion, early targeted therapy based on final culture and /or molecular results is likely the optimal approach to appropriately start broad-spectrum antibiotics. Critical elements in the decision-making process of antibiotic choice include thorough knowledge of guidelines, identification of common pathogens based on the infection source, previous carriage of MDROs or prior antimicrobial exposure, and an understanding of the epidemiology of MDROs in the country, hospital, and the critical care unit (Fig. 1). The decision should also be individualized according to the patient clinical severity and the estimated cost–benefit ratio of each strategy. Utilizing microbiological laboratories and rapid diagnostic tests for prompt microbiological diagnosis may reduce the empirical use of broad-spectrum antimicrobials or allow a prompt de-escalation. Improvement in clinical status and results of cultures performed before initiating treatment should lead to antimicrobial rationalization and de-escalation within 24–72 h. It is advisable to have a multidisciplinary antibiotic stewardship team assist in this process.

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Declarations

Conflicts of interest
JFT reported adboard participation: Merck, Pfizer, BD, Advanz, Menarini, Roche diagnosis, lectures: Merck, Shionogi, Pfizer, Biomerieux, Mundipharma, BD and grants to my research unit: Merck, Pfizer. Unrelated to the submitted works. SSK reported Speaker and advisory board member for Merck, Pfizer, Menarini, Hikma. PD have nothing to report.

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